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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/043,440	01/10/2002	Costas D. Maranas	P05468US1	1336
27407	7590	09/28/2006	EXAMINER	
MCKEE, VOORHEES & SEASE, P.L.C. ATTN: PENNSYLVANIA STATE UNIVERSITY 801 GRAND AVENUE, SUITE 3200 DES MOINES, IA 50309-2721			MORAN, MARJORIE A	
			ART UNIT	PAPER NUMBER
			1631	

DATE MAILED: 09/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No. 10/043,440	Applicant(s) MARANAS ET AL.	
	Examiner Marjorie A. Moran	Art Unit 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 7/28/06.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-16, 19-27 and 29-33 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-16, 19-27 and 29-33 is/are rejected.
- 7) ☒ Claim(s) 22 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/28/06 has been entered.

An action on the merits of pending claims 1-16, 19-27, 29-33 follows. All rejections and objections not reiterated below are hereby withdrawn in view of the claim amendments filed 7/28/06.

***Claim Objections***

Claim 22 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 22 is directed to a system but depends from claim 1, which is a method, and therefore does not further limit the METHOD of claim 1. For purposes of further examination, claim 22 is interpreted as if it recite "The method of claim 1...".

Claim 7 is objected to because of the following informalities: the term --of-- should be inserted after "violation" in line 2. Appropriate correction is required.

***Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-8, 10-15, 19-27, 29-31, and 33 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1-8, 10-15, 20-22, 23-27, and 29-33 are directed to methods for modeling cellular metabolism of an organism comprising steps of in silico modeling and mathematical manipulation. The claims do not recite or result in a physical transformation matter. It is noted that “engineering a change in an organism” as recited in claims 16 and 32, is interpreted to be a physical step based on previous arguments. As claims 16 and 32 do recite a physical transformation of matter, they are directed to statutory subject matter and are not rejected herein. Where a claimed method does not result in a physical transformation of matter, it may be statutory where it recites a concrete, tangible and useful result; i.e. a practical application. The final step of each method claimed is one of “applying” constraints to a model; i.e. of mathematical manipulation. None of the claims recites an actual, concrete result (e.g. an altered model). Further, none of the claims recites communicating a result in a tangible format to one performing the method (e.g. display of the altered model to a user), therefore the claims fail to recite a concrete, tangible, and useful result. As none of claims 1-8, 10-15, 19-27, 29-31, and 33 recite either a physical transformation of matter or a concrete, tangible and useful result, they are not directed to statutory subject matter and are rejected. For a recent update of statutory subject matter, applicant is invited to review

the Guidelines for Patent Eligible Subject matter published in an OG Notice issued 22 November 2005.

Claim 19 is directed to a system comprising a model and a plurality of logic constraints. No physical limitations of the "system" are recited, such that the system is necessarily a physical (man-made) object. The "system" therefore appears to comprise merely data, which is nonfunctional descriptive material. Nonfunctional descriptive material, such as data *per se*, is not statutory subject matter, therefore claim 19 is also rejected. See MPEP 2106 for a discussion of nonfunctional descriptive material.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16, 19-22, and 29-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

Application of logic constraints to "tighten the boundaries for available flux distribution" as recited in amended claims 1, 6, 19, 30 is new matter. Application of logic constraints to "tighten the stoichiometric boundaries" as recited in new claim 33 is

also new matter. Original claims 1, 6, 23, 29, and 30 recited a step of applying logic constraints to a flux balance analysis model, but did not limit the application to produce any desired outcome. Original claim 19 recited logic constraints to be applied in the claimed system, but also failed to recite any desired purpose or outcome resulting from the application of constraints. None of the original claims recited any limitation involving "boundaries."

The originally filed specification, on page 8, discloses that the present invention involves a process for tightening flux boundaries "derived through flux balance models" but does not disclose that boundaries in the model itself are to be tightened, nor is there any disclosure for how the boundaries are tightened nor for any specific step which results in tightening the boundaries. Page 14 of the originally filed specification discloses that additional logic constraints may be applied to a model "to further "tighten" the predictions of flux balance models." The phrase "tighten" in this context is interpreted by the examiner to mean "improve" or "increase the accuracy of." Increasing the accuracy of a model is not the same as tightening stoichiometric boundaries nor boundaries for flux distributions. The instant specification does not disclose anything with regard to the "stoichiometric boundaries" anywhere. The term "flux boundaries" is supported by the specification, on page 8; however, the term "flux boundaries" is different in scope and meaning than "stoichiometric boundaries," therefore the disclosure for "flux boundaries" does not provide support for "stoichiometric boundaries." For this reason, the claims which recite "stoichiometric boundaries" recite new matter for this reason as well as for reciting "tightening" of the boundaries.

In the response filed 7/28/06, applicant points to original claims 1 and 8 for support for new claim 33; however, the original claims did not recite any limitation of “stoichiometric boundaries.” Applicant does not point to support anywhere for the newly recited limitations of application of logic constraints to “tighten the boundaries for available flux distribution” or to “tighten stoichiometric boundaries” and none is apparent, as set forth above, therefore claims 1-16, 19-22, and 29-33 recite new matter and are rejected.

The limitation that “at least a subset” of logic constraints are capable of protecting against violation of a kinetic barrier, as recited in amended claims 2 and 21, is also new matter. Original claim 2 recite selection of constraints to protect against violation of a barrier, but did not limit the selection to be for “at least a subset.” The originally filed specification does not provide support anywhere for a “at least a subset” of constraints which protect against violation of a kinetic barrier. In the response filed 7/28/06, applicant does not point to support for the newly recited limitation, and none is apparent, as set forth herein, therefore claims 2 and 21 are also rejected for this reason.

Logic constraints which include “DNA experimental data constraints,” as recited in claim 22, are new matter. Original claims 1 and 19 limited constraints to include “differential DNA microarray experimental data constraints.” The originally filed specification also discloses “differential DNA microarray experimental data constraints” in various places. Nowhere do the original claims or specification recite or disclose

"DNA experimental data constraints" which are NOT derived from "differential ...microarray" experiments. It is recognized that the new matter may be due to a typographical error; however, as the limitation recited in claim 22 are different in scope than that originally disclosed/recited, claim 22 recites new matter.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-16, 19-27, 29-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 6, 19, 23, 29, 30, and 33 recite in each preamble "modeling cellular metabolism of an organism" but the steps/instructions of the claims fail to recite any relationship of an FBA model to an organism. As it is unclear what relationship is intended between the preamble of each claim and the actual steps/limitations recited, the claims are indefinite. Claims 2-5, 7, 8, 10-15, 20-22, 24-27, and 31 depend from one of claims 1, 6, 23, 29, and 30, and fail to overcome the indefiniteness of the parent claims, and are therefore also indefinite.

Claims 4, 14, 26, 27, 30, and 31 recite a step of applying mixed integer linear programming, but do not recite what the programming is to be applied TO. As it is unclear to what the programming is intended to be applied; i.e. the model, one or more equations representing flux balance, logic constraints, etc., the claims are indefinite.

Claims 4, 5, 14, 15, 26, 27, 30, and 31 recite "to solve (solving) for a desired metabolic outcome" but do not recite WHAT is to be solved. Generally, those of skill in the art apply the term "solving" to equations or other problem for which a solution is unknown or uncertain. The instant claims do not recite any equations. The claims do recite a flux balance analysis model, but if the intention is to "solve" the model, it is unclear what a "solution" of the model is intended to be. As the step(s) or limitation(s) intended by "to solve (solving) for a desired metabolic outcome" is/are unclear, the claims are indefinite.

Claims 16 recites the limitation "the change" in lines 1-2. There is insufficient antecedent basis for this limitation in the claims, therefore claim 16 is indefinite. Parent claims 6 and 12 do not recite any "change" in an organism, and thus fail to provide antecedent basis for the term.

Claims 16 and 32 recite engineering a change in "an organism." It is unclear whether the "organism" in which the change is to occur is the same as the organism recited in the preamble of each of parent claims 6 and 30, respectively, therefore the claims are indefinite.

Claims 16 and 32 recite that a change is to be engineered in an organism "based on" a desired metabolic outcome. The relationship between the engineered change and the desired metabolic outcome intended by the phrase "based on" is unclear. Specifically, it is unclear whether the engineered change is intended to cause or result in the desired metabolic outcome in the organism or is merely a change having some

unspecified degree of relationship to metabolism. As it is unclear what is intended by the phrase "based on", the claims are indefinite.

Claim 30 limits a desired metabolic outcome to be "associated with" an organism. It is unclear whether the metabolic outcome is to be achieved by the organism, or whether the organism is merely one step in a chain which ultimately results in a metabolic outcome, or is the metabolic outcome results etc.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-8, 12-15, 19, 22-23, 25-27, and 29-33 are rejected under 35 U.S.C. 102(e) as being anticipated by PALSSON at al. (US 2002/0012939, filed 2/2/1999).

PALSSON teaches modeling cellular metabolism utilizing stoichiometric mass balances (para's 31-34), and teaches application of constraints (para's 40-45) which result in a restricted (tightened) model (para 40), thereby anticipating claims 1, 6, 19, 23, and 33. These constraints may include those which are required to meet maintenance requirements with regard to energy (kinetic) requirements; i.e. prevent

violation of a kinetic barrier (para 43) or may include "connectivity" constraints; i.e. constraints including information with regard to connections between fluxes inside and outside the cell (para 45); thereby anticipating claims 2-3, 7, 21, and 25. The constraints are those which relate reaction fluxes and metabolic concentrations of analytes in a network (para 45), therefore claim 8 is anticipated. PALSSON also teaches use of mixed integer linear programming (para's 44-46), use of differential DNA microarray data (para 60), and solving for desired metabolic outcomes (para 41 and Examples, pp. 5-6), thereby anticipating claims 4-5, 14-15, 19, 22, 26-27, and 29-31. PAULSSON teaches determination of minimal media for growth of an organism, which is inherently a teaching for identifying a minimal set of metabolic reactions (para 61), and teaches determining the effect of "deletions" in his model (Example 2, p. 6), which is also inherently a teaching for calculating a minimal set of reactions necessary for growth, which teachings anticipate claims 12-13.

### ***Conclusion***

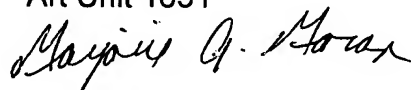
Claims 1-16, 19-27, 29-33 are rejected; claim 22 is also objected to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marjorie A. Moran whose telephone number is (571) 272-0720. The examiner can normally be reached on Monday-Friday; 6 am-2:30 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571)272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Marjorie A. Moran  
Primary Examiner  
Art Unit 1631



9/20/06